

AMENDED CLAIMS

[received by the International Bureau on 10 December 1999 (10.12.99);
original claims 1, 6, 11, 12, 18, 25, 30, 53, 54 and 59 amended;
remaining claims unchanged (12 pages)]

1. A formulation comprising a non-gaseous
5 preparation of FSH or a FSH variant, containing an alpha and
beta subunit, with a preservative selected from the group
consisting of phenol, m-cresol, p-cresol, o-cresol,
chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl,
propyl, butyl and the like), benzalkonium chloride,
10 benzethonium chloride, sodium dehydroacetate and thimerosal,
or mixtures thereof in an aqueous diluent.

2. A formulation of Claim 1, wherein the
preservative is phenol, m-cresol, chlorocresol, or a mixture
thereof.

15 3. A formulation of Claim 2, wherein the
concentration of FSH or a FSH variant is about 1.0 µg/ml to
about 50 mg/ml.

4. A formulation of Claim 3, further comprising
an isotonicity agent.

20 5. A formulation of Claim 4, further comprising
a physiologically acceptable buffer.

6. A formulation comprising a non-gaseous
preparation of FSH or a FSH variant lyophilized in a first
vial, and a second vial containing a preservative selected
25 from the group consisting of phenol, m-cresol, p-cresol, o-
cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl,
ethyl, propyl, butyl and the like), benzalkonium chloride,
benzethonium chloride, sodium dehydroacetate and thimerosal,
or mixtures thereof in an aqueous diluent.

30 7. A formulation of Claim 1, wherein said FSH or
a FSH variant and preservative are in solution.

8. A formulation of Claim 1, wherein said FSH or
a FSH variant is at least one compound selected from the
group consisting of:

35 (a): α-subunit: (SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:2)

5 RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α -subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β -subunit: (SEQ ID NO:4)

10 NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNDSSTDCTVRGLGPSYCSFGDMKE

(c): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

15 β -subunit: (SEQ ID NO:6)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d): α -subunit: (SEQ ID NO:7)

20 FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:8)

NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α -subunit: (SEQ ID NO:9)

25 FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:10)

RSCELTNITITVEKEECDFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIRE

30 (f): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:11)

35 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

FOOTNOTES

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β-subunit: (SEQ ID NO:12)

(h) : α -subunit: (SEQ ID NO:5)

10

β-subunit: (SEQ ID NO:13)

10. A method of Claim 9, wherein said

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--preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof, in an aqueous diluent.

AMENDED SHEET (ARTICLE 19)

comprises a label which indicates that said solution may be held over a period of 24 hours or greater.

13. The article of manufacture of Claim 12, wherein said vial is a glass container having a stopper for multi-use administration.

14. The article of manufacture of Claim 12, wherein said vial is a blister pack, capable of being punctured and used in pulmonary administration.

15. The article of manufacture of Claim 12, wherein said vial is a pen-injector device.

16. An article of manufacture, comprising packaging material, a first vial comprising lyophilized FSH or a FSH variant, containing an alpha and beta subunit, and a second vial comprising a preservative solution, wherein said packaging material comprises a label which instructs a patient to reconstitute the said lyophilized FSH or a FSH variant in the preservative solution for use over a period of of 24 hours or greater.

17. The article of manufacture of Claim 16, wherein said first vial and said second vial are embodied in a pen-injector device.

18. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a preserved solution of a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit, said solution being suitable for administration over a period of 24 hours or greater.

19. A method of using a stable solution of FSH or a FSH variant, containing an alpha and beta subunit to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of FSH or a FSH variant in a stable solution, said solution being suitable for administration over a period of 24 hours or greater.

20. The use of at least one alpha or beta polypeptide of a FSH or a FSH variant in the preparation of

a preserved formulation adapted for administration over a period of 24 hours or greater.

21. A stable formulation comprising at least one FSH or a FSH variant, containing an alpha and beta subunit, and phosphate buffer containing saline or a salt, wherein said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

22. A formulation of Claim 21, wherein the concentration of said FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

23. A formulation of Claim 21, further comprising an isotonicity agent.

24. A formulation of Claim 21, wherein said buffer is phosphate buffered saline.

25. A formulation comprising a first vial containing a nongaseous preparation of FSH or a FSH variant containing an alpha and beta subunit, and a second vial containing phosphate buffer containing saline or a salt.

26. A formulation of Claim 21, wherein said FSH or a FSH variant and said phosphate buffer are in solution.

27. A formulation of Claim 21, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit:(SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit:(SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α-subunit:(SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYIQCKGCCFSRAYPTPARSRKTMMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit:(SEQ ID NO:4)

NSCELTNITIAVEKEGCGFCITINTTWAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNDSSTDCTVRGLGPSYCSFGDMKE

(c): α -subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit:(SEQ ID NO:6)

5 NSCELTNITIAIEKEECCRFCISINTTWCAGYCYTRDLVYKDPARPPIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d): α -subunit:(SEQ ID NO:7)

FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

10 β -subunit:(SEQ ID NO:8)

NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α -subunit:(SEQ ID NO:9)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
15 ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit:(SEQ ID NO:10)

RSCELTNITITVEKEECSCFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKE
LVYETVKVPGCAHHADSLYTPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIR
E

20 (f): α -subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit:(SEQ ID NO:11)

NSCELTNITIAIEKEECCRFCISINTTWCAGYCYTRDLVYKDPARPPIQKTCTFKEL
25 VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g): α -subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit:(SEQ ID NO:12)

30 NSCELTNITIAIEKEECCRFCISINTTWCAGYCYTRDLVYKDPARPPIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h): α -subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

35 β -subunit:(SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSSTDCTVRGLGPSYCSFGEMK

28. A method of treating infertility which
5 comprises administering to a patient in need thereof a
formulation according to Claim 21.

29. A method of Claim 28, wherein said
patient is selected from the group consisting of a human,
sheep, cow, pig, horse, or rabbit.

10 30. A process for preparing a stable solution
formulation of FSH or a FSH variant, containing an alpha and
beta subunit, which comprises admixing a non-gaseous
preparation of FSH or a FSH variant with a phosphate buffer
containing saline or a salt.

15 31. An article of manufacture for pharmaceutical
use, comprising packaging material and a vial comprising a
stable solution of FSH or a FSH variant, containing an alpha
and beta subunit, in an aqueous diluent, wherein said
packaging material comprises a label which indicates that
20 such solution is suitable for use over a period of 24 hours
or greater.

32. The article of manufacture of Claim 31,
wherein said vial is a glass container having a stopper for
multi-use administration.

25 33. The article of manufacture of Claim 31,
wherein said vial is a blister pack, capable of being
punctured and used in pulmonary administration.

34. The article of manufacture of Claim 31,
wherein said vial is a pen-injector device.

30 35. An article of manufacture, comprising
packaging material, a first vial comprising a lyophilized
FSH or a FSH variant containing, an alpha and beta subunit,
and a second vial comprising a stable aqueous diluent,
wherein said packaging material comprises a label which
35 instructs a patient to reconstitute said FSH or a FSH

variant in the aqueous diluent to form a solution that is suitable for use over a period of 24 hours or greater.

36. The article of manufacture of Claim 35, wherein said first vial and said second vial are embodied in a pen-injector device.

37. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, in an aqueous phosphate buffered diluent, said solution being suitable for administration over a period of 24 hours or greater.

38. A method of using a solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant in an aqueous diluent suitable for use over a period of 24 hours or greater.

39. The use of at least one polypeptide of a FSH or a FSH variant in the preparation of a stable formulation adapted for administration over a period of 24 hours or greater.

40. A formulation as described herein.

41. An article of manufacture as described herein

42. A process as described herein.

43. A use as described herein.

44. A method as described herein.

45. Use of a formulation of claim 1 for treating infertility in a patient in need thereof.

46. Use of a formulation of claim 1 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

47. Use of a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, said solution being suitable for administration over a period of 24 hours or greater.

48. Use of a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of said FSH or a FSH
5 variant in a phosphate buffer, containing saline or a salt, over a period of 24 hours or greater.

49. Use of a formulation of Claim 21 for treating infertility in a patient in need thereof.

50. A use of Claim 49 wherein said patient is
10 selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

51. Use of stable stable solution of purified FSH or a FSH variant, containing an alpha and beta subunit, in a phosphate buffer containing saline or a salt suitable for
15 administration over a period of 24 hours or greater for treating infertility in a patient in need thereof.

52. Use of a stable solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, wherein said
20 stable solution of said FSH or a FSH variant in phosphate buffer containing saline or a salt is suitable for use over a period of 24 hours or greater.

53. A process of producing a formulation comprising admixing a non-gaseous preparation of FSH or a
25 FSH variant, containing an alpha and beta subunit, and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium
30 dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

54. A process of producing a stable formulation comprising admixing at least a non-gaseous preparation of FSH or a FSH variant, containing an alpha and beta subunit,
35 and a phosphate buffer containing saline or a salt, wherein

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said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

55. A process of Claim 53, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

56. A process according to any of Claims 53-54, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

57. A process according to any of Claims 53-54, further admixing an isotonicity agent.

58. A process of Claim 53-54, further admixing a physiologically acceptable buffer.

59. A process comprising preparing a a non-gaseous preparation FSH or a FSH variant lyophilized in a first vial, and preparing a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

60. A process of Claim 59, wherein said FSH or a FSH variant and preservative are further put into solution.

61. A process according to any of claims 53-54, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit: (SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMVLVPMK
ITSEATCCVAKAFATKATVMGNVRVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α-subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSRKTMVLVPMK
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β -subunit:(SEQ ID NO:4)

NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNSTDCTVRGLGPSYCSFGDMKE

(c): α -subunit:(SEQ ID NO:5)

5 APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit:(SEQ ID NO:6)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

10 (d): α -subunit:(SEQ ID NO:7)

FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

β -subunit:(SEQ ID NO:8)

15 NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α -subunit:(SEQ ID NO:9)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit:(SEQ ID NO:10)

20 RSCELTNITITVEKEECSEFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIRE

(f): α -subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

25 β -subunit:(SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g): α -subunit:(SEQ ID NO:5)

30 APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit:(SEQ ID NO:12)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h): α -subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSSTDCTVRGLGPSYCSFGEMK

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